



DIABETIC KIDNEY DISEASE:

MANAGING RISK AND SLOWING PROGRESSION

Topics

- › Evaluation of Patients with DKD
- › Management of DKD: Kidney and Heart Outcomes

Evaluation of Patients with DKD

Chronic kidney disease (CKD) carries a higher risk for mortality and is associated with multiple comorbid conditions, including cardiovascular disease (CVD).^{1,2} Diabetes is the leading cause of CKD and accounts for 38% of new cases of end-stage kidney disease (ESKD).³ Multiple complications are associated with diabetes, including retinopathy and neuropathy. Diabetes is also a major risk factor for CVD and can lead to other vascular organ complications, including diabetic kidney disease (DKD) or diabetic nephropathy.^{4,5,6,7} Because of these relationships, patients with diabetes should be screened annually for kidney disease (Table 1).

CKD is defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/m² or markers of kidney damage for >3 months.¹ DKD is a clinical diagnosis based upon the presence of albuminuria, decreased eGFR, or both, in the presence of diabetes (the majority being patients with type 2 diabetes). Detection of elevated urinary albumin excretion (UACR) and decreased eGFR are the main markers for the presence of DKD or CKD.⁶

Elevated UACR and reduced eGFR have been shown to be independent risk factors for progressive ESKD, CVD, and mortality.^{1,8,9} Therefore, both should be measured to properly assess stage of kidney disease. A meta-analysis of general population cohorts indicated that declining eGFR and elevation of UACR are independent predictors of cardiovascular (CV) mortality risk in the general population.¹⁰ The study indicates that CKD, particularly in the presence of albuminuria above 300 mg/day, should be considered an additional CV risk factor.^{4,7} The CVD risk in people with diabetes is even higher with the presence of CKD. One meta-analysis study found that the risk for CV mortality was 1.2–1.9 times higher in participants with diabetes than in those without diabetes, across the entire range of eGFR and UACR.¹¹

Using hemoglobin A1c (HbA1c) to monitor glycemic control in patients with DKD is recommended. Monitoring long-term glycemic control by measuring HbA1c twice per year is considered reasonable for patients with diabetes, and it can be measured as often as 4 times per year if the glycemic target is not met or after a change in antihyperglycemic therapy.¹²

Table 1: Screening for CKD in Patients with Type 2 Diabetes

When to screen: <ul style="list-style-type: none">• At diagnosis of type 2 diabetes
Screening tests: <ul style="list-style-type: none">• eGFR from serum creatinine measurement• Albumin-to-creatinine ratio (ACR) in a spot urine sample<ul style="list-style-type: none">• ACR 30-300 mg/g: Moderately high albuminuria• ACR >300 mg/g: Severely high albuminuria
Screening frequency: <ul style="list-style-type: none">• Annual

NKF KDOQI. *Am J Kidney Dis.* 2007;49:S1-S179.⁶

KDIGO. *Kidney Int.* 2020;98:S1-S115.¹²

Management of DKD: Kidney and Heart Outcomes

DKD is a complex chronic disease that typically requires multiple intervention strategies, including glycemic control, lifestyle modifications (e.g., low-sugar diet, physical activity), and control of CVD-related risk factors (e.g., blood pressure, lipids, albuminuria).

Drugs that interact with the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), can be applied to both manage blood pressure and slow kidney disease progression.^{6,7} RAAS blockade agents have been shown to reduce blood pressure, decrease the risk of CV events, reduce albuminuria, and help slow the progression of kidney disease in patients with DKD.^{13,14,15,16,17} Additional measures to help preserve kidney function can also include avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) and caution with the use of certain contrast dyes with imaging tests.

People with DKD are at high CV risk; therefore, statins should be considered.^{7,12} However, statins have not been shown to reduce the risk of CV events or mortality in patients with eGFR <30 mL/min/1.72 m², including dialysis patients and, thus, are not recommended in such patients.^{7,18} Patients with DKD can be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their CV and physical tolerance.¹²

Glycemic control is a crucial part of diabetes management. People with DKD do not represent a uniform population, so individual circumstances must be incorporated into therapeutic targets. The approach to target an HbA1c of <7.0%, if tolerated, has been similar in patients with type 1 and type 2 diabetes. However, it should be noted that the risk of hypoglycemia with intensive glucose control is greater among patients with reduced eGFR, particularly those treated with insulin or sulfonylureas. A target HbA1c >7.0% is recommended for patients with comorbidities or limited life expectancy.⁶ An HbA1c target ranging from <6.5% to <8.0% has been recommended in patients with DKD not treated with dialysis, while incorporating elements of decision making based on individual patient characteristics (Figure 1).¹²

Multiple medications are often used to help patients with type 2 diabetes achieve a desired level of glycemic control, including insulins, biguanides, sulfonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, dopamine-2 agonists, amylin mimetics, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors.¹⁹ A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences, particularly with insulin and sulfonylureas.^{7,19} SGLT2 inhibitors have been recommended if CKD or heart failure is present, independent of glycemic control.¹⁹

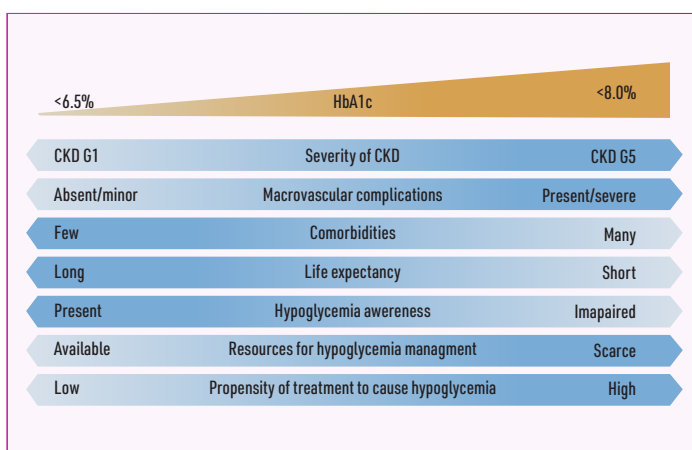
Initial treatment with metformin has been recommended in patients with type 2 diabetes,¹⁹ including those with CKD and an eGFR >30 mL/min/1.73 m².¹² Monitoring frequency should be increased when the eGFR is <60 mL/min/1.73 m², and the dose should be adjusted when the eGFR is <45 mL/min/1.73 m².¹² Patients should be monitored for vitamin B12 deficiency when treated with metformin for >4 years.

In many cases, patients may need additional therapies to achieve desired glycemic control, and people with DKD are at higher risk for CVD and progressive kidney disease. Newer diabetic therapies (e.g., SGLT2 inhibitors, GLP-1 agonists) have been studied for their ability to improve heart or kidney outcomes in people with diabetes through mechanisms beyond glycemic control.

SGLT2 inhibitors target sodium glucose co-transporter-2, which is part of a class of membrane-bound proteins that reabsorbs glucose back into the body from urine.^{20,21} Data indicate that medications within this class can reduce hospitalization for heart failure.^{22,23,24,25} Reductions in CV events with the use of SGLT2 inhibitors have been shown in the trials EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and CANVAS (Canagliflozin Cardiovascular Assessment Study).^{26,27}

Secondary, exploratory, or ad hoc analysis of SGLT2 trial data has shown reductions in kidney-related composites (EMPA-REG OUTCOME, CANVAS, DECLARE TIMI 58).^{24,28,29,30,31,32} Dedicated clinical trials including patients with type 2 diabetes and CKD receiving an ACEI or ARB have also indicated improved kidney-related outcomes with canagliflozin (CRENDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) and dapagliflozin (DAPA-CKD: Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease).^{33,34} These drugs are effective in reducing kidney disease progression down to an eGFR of 25 mL/min/1.73 m², but their ability to reduce glucose levels is relatively minor when the eGFR is <45 mL/min/1.73 m². This indicates that mechanisms other than glycemic control are involved in the kidney disease benefits. SGLT2 inhibitors have been recommended for use in patients with type 2 diabetes and CKD. SGLT2 inhibitors with documented kidney or CV benefits should be prioritized, taking eGFR into account.¹²

Figure 1: Factors Guiding Decisions on Individual HbA1c Targets



CKD, chronic kidney disease; G1, estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m²; G5, eGFR <15 mL/min/1.73 m²; HbA1c, glycated hemoglobin. KDIGO. *Kidney Int.* 2020;98:S1-S115.12

GLP-1 agonists target the glucagon-like peptide 1 receptor.³⁵ GLP-1 agonists can affect glucose levels through several mechanisms, including increased glucose-dependent insulin secretion, slowed gastric emptying, and lower postprandial glucagon.³⁶ Studies have indicated benefits of GLP-1 agonists beyond glycemic control, including blood pressure reduction and weight loss.^{36,37} CV outcome studies have shown significant CV benefits for liraglutide, dulaglutide, and semaglutide.^{38,38,40} Secondary, exploratory, or ad hoc analysis of these trials designed for CV outcomes indicate that GLP-1 agonists may have a benefit on kidney-related outcomes and can reduce albuminuria in patients with diabetes.^{41,42,43,44}

In a trial designed to assess glycemic control in patients with moderate-to-severe CKD, dulaglutide in combination insulin lispro attenuated progression of kidney disease.⁴⁵ The FLOW (Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and CKD) trial is the first randomized statistically powered endpoint study to assess effect on primary kidney-related outcomes in DKD.⁴⁶ In patients with type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin and an SGLT2 inhibitor, or who are unable to use those medications, a long-acting GLP-1 agonist has been recommended.¹² GLP-1 agonists with documented CV benefits should be prioritized.¹²

DKD is a complex and heterogeneous disease with numerous overlapping etiologic pathways, and research is ongoing to discover and develop additional DKD therapies.¹⁸ For example, finerenone is a novel, selective, non-steroidal mineralocorticoid receptor antagonist (MRA) that inhibits inflammation and fibrosis and protects against progressive kidney and CV dysfunction in preclinical models.^{47,48} Finerenone is under review by the US FDA for use in patients with CKD and type 2 diabetes. The Phase III FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial included nearly 5,800 patients with type 2 diabetes and either severely or moderately elevated albuminuria plus retinopathy and were randomly assigned to finerenone or placebo and receiving an ACEI or ARB.⁴⁹ The study showed that those taking finerenone had lower risks of CKD progression and CV events than placebo. During a median follow-up of 2.6 years, a primary outcome event (ESKD, a sustained decrease of 40% in eGFR from baseline, kidney-related mortality) occurred in 17.8% of the finerenone group and 21.1% of the placebo group (HR, 0.82; 95% CI, 0.73 - 0.93; P = 0.001).⁴⁹

In summary, the advent of novel agents with several possible mechanisms of action independent of glucose lowering may offer potential benefits beyond glycemic control in DKD.

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